SHORT REPORT

Range of cross reactivity of anti-GM1 IgG antibody in Guillain-Barré syndrome

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Abstract

The cross reactivity of anti-GM1 IgG antibody with various gangliosides and asialo-GM1 in serum samples from 27 patients with Guillain-Barré syndrome was investigated. An enzyme linked immunosorbent assay (ELISA) absorption study showed that anti-GM1 IgG antibody cross reacted with asialo-GM1 in 52% of the patients, GM1b in 41%, GD1b in 22%, and GalNAc-GD1a in 19%, and that it did not cross react with GM2, GT1b, or GQ1b. The antibody that cross reacted with GD1b was associated with a high frequency of cranial nerve involvement and negative *Campylobacter jejuni* serology. Anti-GM1 IgG antibody has a broad range of cross reactivity which may contribute to various clinical variations of Guillain-Barré syndrome.

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Guillain-Barré syndrome (GBS) is an autoimmune mediated neuropathy that has various neurological presentations. Evidence indicates that the presence of antiganglioside antibody is closely related to the clinical and electrophysiological features of GBS. Patients with anti-GM1 antibody often have a motor axonal neuropathy, but they rarely show sensory disturbance and cranial nerve involvement.[1–3] In addition, anti-GM1 antibody is closely associated with prior infection by *Campylobacter jejuni*.[2 4] Patients with anti-GM1 IgG antibody, however, do not always have these features. Antecedent upper respiratory tract infection, cranial nerve deficits, and sensory loss have been found respectively in 25%, 31%, and 19% of patients with this antibody.[3]

The coexistence of serum anti-GM1 antibody and antibodies to other gangliosides and asialo-GM1 occurs in some patients with GBS (reviewed by Hartung *et al*[5]), indicative that the cross reactivity of these antibodies is due to structural homology. Anti-asialo-GM1 and anti-GD1b antibodies in particular, are often found in patients with anti-GM1 IgG antibody. These antibodies seem to recognise a sugar sequence (Gal β 1–3 GalNAc β 1–4 Gal) that is common to GM1, asialo-GM1, and GD1b. Further investigation, however, is needed to determine the antibody cross reactivity, and the range of cross reactivity of the anti-GM1 IgG antibody has yet to be clarified. Susuki *et al*[6] have shown that fine specificity of anti-GQ1b IgG antibody is closely related to the clinical manifestations; deep sense disturbance is significantly present when anti-GQ1b antibody cross reacts with GD1b. We assume that the anti-GM1 IgG antibody has different fine specificities, which contribute to the various clinical manifestations seen in patients with GBS with anti-GM1 IgG antibody. The aims of this study were to clarify the range of cross reactivity of anti-GM1 IgG antibody and to examine its relation with clinical features.

Methods

We carried out an absorption study to examine the cross reactivity of serum anti-GM1 IgG antibody with various gangliosides (GM2, GM1b, GD1a, GalNAc-GD1a, GD1b, GT1b, and GQ1b) and asialo-GM1 using serum from 27 patients with GBS who tested positive for anti-GM1 IgG antibody in an enzyme linked immunosorbent assay (ELISA) (normal titre<500).[7] Diagnosis of GBS was based on the established clinical criteria.[8] The absorption study was done as described elsewhere[7] with microtitre plates coated with 5 pmol portions of ganglioside or asialo-GM1. Serum samples were added to the wells at the dilution which gave an optical density between 1.0 and 2.0. After incubation at 4°C overnight, the samples were used as the primary antibodies in the standard enzyme linked immunosorbent assay. Absorption rates were expressed as percentages of the optical densities obtained with and without absorption. All results were confirmed twice to reduce technical bias.

Results

Anti-GM1 IgG antibody was absorbed effectively (20% or more absorption rate) by asialo-GM1 in 14 (52%) of 27 patients, GM1b in 11 (41%), GD1b in six (22%), and GalNAc-GD1a in five (19%, fig 1). The antibody was not absorbed by GM2, GT1b, or GQ1b. In 10 (37%) of the 27 patients, anti-GM1 IgG antibody was not absorbed by any of the gangliosides or by asialo-GM1. Clinical features were not associated with antibody cross reactivity with any of the gangliosides or asialo-GM1, except for GD1b. Patients with anti-GM1 IgG antibody that cross reacted with GD1b more often had facial and bulbar palsies

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Table 1 Cross reactivity of anti-GM1 IgG antibody with GD1b and clinical features of GBS

	Cross reactivity with GD1b				
	Present (n=6)*	*Absent (n=21)*	*p Value†*	*Odds ratio*	*95% Confidence interval*
Sex (male/female)	5/1	12/9	0.25		
Median age (y)	47	43	0.35		
Diarrhoea	2 (33%)	14 (67%)	0.16		
URTI‡	5 (83%)	5 (24%)	0.02	16	2.1–123
Ophthalmoplegia	1 (17%)	0	0.22		
Facial palsy	2 (33%)	0	0.04	24	2.5–231
Bulbar palsy	3 (50%)	0	0.01	43	5.0–367
Sensory disturbance	2 (33%)	6 (29%)	0.59		
C jejuni infection	2 (33%)	18 (86%)	0.02	0.083	0.013–0.55

*Absorption rate, 20% or more.
†Tested by Fisher's exact test. A p value< 0.05 was considered significant.
‡Upper respiratory tract infection.

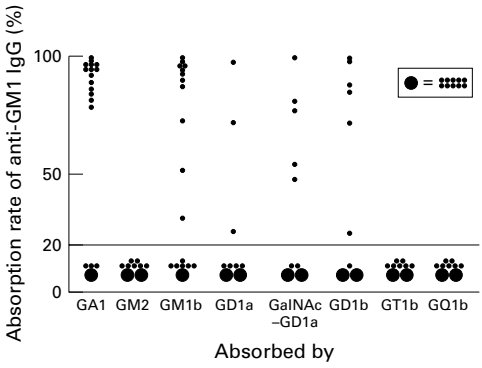

Figure 1 Absorption rates of anti-GM1 IgG antibody by various gangliosides and asialo-GM1 (GA1).

than those with unreacting antibody (table 1). Three of six patients with anti-GM1 IgG antibody that cross reacted with GD1b had bulbar palsy, and two of them needed artificial ventilation. Severe axonal degeneration of facial and vagal nerves was confirmed by necropsy in one of them. When anti-GM1 IgG antibody cross reacted with GD1b, there was often a history of antecedent upper respiratory tract infection, and serological evidence of recent *C jejuni* infection was rare. These associations between cross reactivity and clinical features were valid, even when the cut off values for judging "cross reactive" were defined as absorption rates of 5%, 10%, and 30%, rather than 20%.

Discussion

We showed that anti-GM1 IgG antibody in GBS has a broad range of fine specificity. As expected, in some patients the antibody cross reacted with asialo-GM1 and GD1b, which have a sugar sequence in common with GM1 at the non-reducing terminal. The antibody also recognised GM1b and GalNAc-GD1a which does not have a sugar sequence in common with GM1. Tatsumoto *et al*[9] reported that GM1b and GalNAc-GD1a have a common three dimensional epitope with a stereoscopic structure, whereas they have no sugar sequence in common. Their findings and ours suggest that three dimensional structures, as well as the sugar sequences of gangliosides, are important for cross reactivity of the antiganglioside antibody with various gangliosides.

Of the various fine specificities of the anti-GM1 IgG antibody, only its cross reactivity with GD1b was associated significantly with clinical features; however, the patient population was small. Lack of cranial nerve involvement and antecedent *C jejuni* infection have been regarded as clinical features of patients with GBS with anti-GM1 antibody. Our findings show that these features are closely related to the presence of anti-GM1 IgG antibody, which lacks cross reactivity with GD1b. By contrast, most patients who had anti-GM1 IgG antibody that cross reacts with GD1b had a history of upper respiratory tract infection and negative serology for recent *C jejuni* infection. These findings suggest that some other pathogen(s) that causes respiratory infection is often the antecedent agent of infection in patients with anti-GM1 IgG antibody that cross reacts with GD1b.

Serum anti-GD1b antibody increases in some patients with sensory ataxic neuropathy, and GD1b is a putative target antigen in this disease (reviewed by Dalakas and Quarles[10]). The frequency of sensory disturbance, however, did not differ whether or not anti-GM1 IgG antibody cross reacted with GD1b. Because ours is a retrospective and small study, the association between sensory disturbance and the fine specificity of anti-GM1 antibody needs further clarification.

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1 Rees JH, Gregson NA, Hughes RAC. Anti-ganglioside GM1 antibodies in Guillain-Barré syndrome and their relationship to Campylobacter jejuni infection. *Ann Neurol* 1995;**38**:809–16.
2 Jacobs BC, van Doorn PA, Schmitz PIM, *et al.* Campylobacter jejuni infections and anti-GM1 antibodies in Guillain-Barré syndrome. *Ann Neurol* 1996;**40**:181–7.
3 Kuwabara S, Yuki N, Koga M, *et al.* IgG anti-GM1 antibody is associated with reversible conduction failure and axonal degeneration in Guillain-Barré syndrome. *Ann Neurol* 1998;**44**:202–8.
4 Rees JH, Soudain SE, Gregson NA, *et al.* Campylobacter jejuni infection and Guillain-Barré syndrome. *N Engl J Med* 1995;**333**:1374–9.
5 Hartung H-P, Pollard JD, Harvey GK, *et al.* Immunopathogenesis and treatment of the Guillain-Barré syndrome: part I. *Muscle Nerve* 1995;**18**:137–53.
6 Susuki K, Yuki N, Hirata K. Fine specificity of anti-GQ1b IgG antibodies and clinical features. *J Neurol Sci* 2001;**185**: 5–9.
7 Koga M, Yuki N, Ariga T, *et al.* Is IgG anti-GT1a antibody associated with pharyngeal-cervical-brachial weakness or oropharyngeal palsy in Guillain-Barré syndrome? *J Neuroimmunol* 1998;**86**:74–9.
8 Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. *Ann Neurol* 1990; **27**(suppl):S21–4.
9 Tatsumoto M, Yuki N, Tateno M, *et al.* Molecular mimicry between GalNAc-GD1a and GM1b. *Muscle Nerve* 1998; (suppl 7):S211.
10 Dalakas MC, Quarles RH. Autoimmune ataxic neuropathies (sensory ganglionopathies): are glycolipids the responsible autoantigens? *Ann Neurol* 1996;**39**:419–22.